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EXAMINER	
ANGELL, JON E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/578,900	Applicant(s) CARULLI ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *3-5 and 8-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7 and 48-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 2/3/03, as Paper No. 20. The amendments to the specification have been entered. The amendment of claim 6 has been entered. New claims 48-61 have been entered. Claims 1-61 are currently pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. For the reasons previously set forth, claims 3-5 and 8-47 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11, filed 3/22/02.

4. Claims 1, 2, 6, 7 and 48-61 are examined herein.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent

Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically the application contains sequence disclosures which are not designated with the appropriate sequence identifiers (SEQ ID NO.). Please see, for example, page 35 (Table 2) of the specification which discloses sequences of primers without sequence identifiers. Please note that all sequence errors must be corrected in order for a response to be considered complete.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Priority

1. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 and/or 121 is acknowledged. However, the provisional applications upon which priority is claimed (60/071449 and 60/105511) fail to provide adequate support under 35 U.S.C. 112 for claims 1, 2, 6 and 7 of this application. The provisional applications do not disclose the sequences of Zmax1, HBM, or the polymorphisms of Zmax1/HBM (i.e. the polymorphisms of Table 4) encompassed by the claims.***Response to Arguments***

2. Applicant's arguments filed 2/3/03 have been fully considered but they are not persuasive. Applicants argue that the provisional application discloses the BAC clone comprising the sequence of the Zmax1 gene. However, the sequence of Zmax1 was not clearly identified in the provisional application, nor are any of the Zmax1 polymorphisms encompassed by the claims. Applicants are asked to identify by specific page and line number where in the

provisional application support for the sequences of HBM, Zmax1, and Zmax1 polymorphisms can be found.

Claim Rejections - 35 USC § 101 & 35 USC § 112

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 6, 7 and 42-61 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility.

8. Claims 1, 2, 6, 7 and 42-61 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. The instant claims are drawn to a method for identifying a molecule involved in lipid regulation comprising identifying a molecule that binds to , or that inhibits the binding of a molecule to, HBM or Zmax1 (see claim 1); as well as a method for identification of candidate molecules involved in lipid regulation by identifying molecules that bind to the nucleic acid of

Zmax1 (SEQ ID NO: 1), or a polymorphism of Table 4 except one specific polymorphism, or an HBM nucleic acid having SEQ ID NO: 2 (see claim 6).

The specification teaches that the nucleic acid sequences encoding the High Bone Mass (HBM) protein of SEQ ID NO:4 are allelic variants of Zmax1 gene. The specification further teaches that protein encoded by HBM (mutated) gene causes elevated bone mass while the protein encoded by Zmax1 (wild type) gene does not (spec. page 18, line 19-24). The specification further teaches Zmax1 gene is common in human population, while HBM gene is rare (spec. page 19 line 3-8). In addition, the specification disclosed the pedigree of the individuals used in genetic linkage analysis and concluded that HBM is an inheritable trait (spec. page 22, line 16 through page 23, line 5; and Example 1).

The specification indicates that Zmax1 is related to the low density lipoprotein receptor (LDL receptor) (see spec. page 83, line 13-25; and p. 125). However, the relationship of Zmax1 to the LDL receptor appears to be based purely sequence homology. There is no disclosure clearly indicating that Zmax1 (or any polymorphism thereof) is actually involved in lipid regulation.

Regarding the involvement of HBM in lipid regulation, the specification indicates that biochemical tests were performed to measure the serum levels of various lipid containing molecules and precursors in affected and unaffected HBM family members to test whether the HBM mutation in the Zmax1 gene affects lipid regulation (see Example 3, starting at p. 125). The specification discloses that triglycerides and VLDL were "generally lower in affected [i.e. HBM+] than unaffected [i.e. HBM-] individuals", while HDL and the ratio of LDL to HDL was "generally higher in affected males than unaffected males" (see p. 126, line 21-27). There is no other disclosure in the specification indicating a link between Zmax1 or HBM and lipid regulation.

Therefore, the only link between Zmax1 and lipid regulation is sequence homology between Zmax1 and the LDL-receptor. The only link between HBM and lipid regulation is the indication that persons with the HBM polymorphism show a generally lower serum level of triglycerides and VLDL and a generally higher serum level of HDL, compared to controls.

Serum lipid regulation is recognized in the art as a very complex process that involves many different factors including diet, as well as the function of many different genes. For instance, Ye et al. (Am. J. Clin. Nutr. 2000; Vol. 72 (Suppl), pages 1275S-1284S) teaches that genes influence quantitative variations in plasma lipoprotein concentrations (see abstract). Specifically, Ye reviews a number of DNA polymorphisms (specifically, polymorphisms in the genes encoding apo A-I, apo A-IV, apo B, apo C-III, apo E, LPL, CETP, LCAT, and LDL receptor) which are thought to be involved in plasmid lipid regulation. However, regarding the effects of the polymorphisms on serum lipid levels, Ye teaches, that the effects of the polymorphisms on lipid metabolism have been inconsistent due to a number of factors. Specifically, Ye teaches,

> "Although more and more data are available on the effects of genetic polymorphisms in genes related to lipid metabolism and the responsiveness to dietary fat and cholesterol, no consistent effects of most reported genetic factors have been seen. The major problems related to these discrepancies are sample size, effects of age and sex, different ethnic and cultural (dietary) backgrounds of the participants, different dietary protocols used, and the difficulty of insuring compliance. More clinical trials in large populations with standardized protocols are needed to study further the effects of these polymorphisms on the responsiveness to dietary fat and cholesterol." (see p. 1282S, first column).

Furthermore, regarding the sequence homology of Zmax1 to the LDL receptor, the art at the time of filing recognized that lipid metabolism was not the only function for LDL receptors. For instance, Willnow et al. (Nature Cell Biol.; Vol. 1, October 1999, pages E157-E162) teaches,

> "Lipoprotein receptors used to be viewed simply as the means by which cells were supplied with lipids for energy production and membrane synthesis. This perception has now changed dramatically. Megalin, a member of the low density lipoprotein receptor gene family, turns out to mediate the endocytic uptake of retinoids and steroids, thus helping to regulate their biological function. Other members of this receptor family interact with cytosolic signaling proteins, giving this evolutionary ancient family of receptors and entirely unexpected new role as transducers of extracellular signals." (see abstract).

Therefore, one of skill in the art would not readily recognize any sequence homologue of the LDL-receptor as a compound which would automatically be involved in lipid regulation without first performing additional experimentation.

The invention as claimed does not have a substantial asserted utility or a well establish utility because the specification fails to disclose the direct involvement of either HBM or Zmax1 in lipid regulation. The art at the time of filing clearly indicates that lipid regulation is a complex process that involves a number of different factors including diet, as well as a number of different genes. Furthermore, the art at the time of filing clearly indicates that LDL-receptor family members can have functions other than lipid regulation. Since the specification fails disclose a single working example that teaches that HBM and/or Zmax1 are directly involved in lipid regulation, it is unclear how one of skill in the art would use HBM or Zmax1 to identify molecules or candidate molecules involved in lipid regulation without performing additional experimentation. Therefore, the asserted use for the claimed molecules (HBM and Zmax1) is not supported by either a substantial or well-established utility. The only immediate apparent utility for the instant molecules would be for the further scientific characterization of their involvement in the lipid regulation, bone development and/or osteoporosis.

Furthermore, should the claimed use of the HBM and Zmax1 be found to be credible specific and substantial (or well-established), without a clear indication of the function of HBM and Zmax1, particularly with respect to lipid regulation, one of skill in the art would still have to perform an undue amount of additionally experimentation in order to use HBM or Zmax1 as claimed. The amount of additional experimentation is deemed to be undue because involvement of HBM and Zmax1 in lipid regulation would have to be established before one could attempt to practice the claimed invention.

10. Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

11. Claim 6 has been amended to recite, "A method for the identification of a candidate molecule involved in lipid regulation comprising: (A) identifying a first molecule that binds to,

or that inhibits binding of a second molecule to, the nucleic acid sequence of a Zmax1 nucleic acid chosen from among the sequences SEQ ID NO: 1 and a Zmax1 nucleic acid compromising a polymorphism of Table 4, except for the C/A base change at location 21119 (308G), or a HBM nucleic acid having SEQ ID NO: 2..."

The specification does not explicitly disclose the negative limitation indicated above. Specifically, the examiner cannot find anywhere in the specification that explicitly indicates that the method can use any Zmax1 polymorphism, except for the C/A polymorphism at location 21119 (308G). Applicants have not indicated the precise location (by page and line number) where the disclosed negative limitation can be found. Applicants are asked to specifically indicate the page and line number where the specific exclusion of polymorphism can be found. Without a clear and explicit disclosure of the method using any of the Zmax polymorphisms of Table 4, except for C/A at 21119 (308G), the claim encompasses new matter which was not disclosed in the specification and a rejection under 35 USC 112, first paragraph is appropriate.

Claim 7 depends on claim 6 and is therefore rejected for the same reasons.

Claim Rejections - 35 USC § 112, second paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 has been amended to recite, "A method for the identification of a candidate molecule involved in lipid regulation comprising: (A) identifying a first molecule that binds to, or that inhibits binding of a second molecule to, the nucleic acid sequence of a Zmax1 nucleic acid chosen from among the sequences SEQ ID NO: 1 and a Zmax1 nucleic acid compromising a polymorphism of Table 4, except for the C/A base change at location 21119 (308G), or a HBM nucleic acid having SEQ ID NO: 2…"

The claim is indefinite because it is unclear if the method is drawn to:

1) identifying a first molecule that binds to, or that inhibits binding of a second molecule to, the nucleic acid sequence of a Zmax1 nucleic acid chosen from among the sequences SEQ ID NO: 1, a HBM nucleic acid having SEQ ID NO: 2, and a Zmax1 nucleic acid compromising a polymorphism of Table 4, except for the C/A base change at location 21119 (308G)…"

or, alternatively, the method could be drawn to:

2) identifying a first molecule that binds to, or that inhibits binding of a second molecule to, the nucleic acid sequence of a Zmax1 nucleic acid chosen from among the sequences SEQ ID NO: 1 and a Zmax1 nucleic acid compromising a polymorphism of Table 4, except for i) the C/A base change at location 21119 (308G), and except for ii) a HBM nucleic acid having SEQ ID NO: 2…"

Because there are at least two different interpretations of the claim, the claim is indefinite and rejection under 35 USC 112, second paragraph is appropriate.

Claim 7 depends on claim 6, and is therefore rejected for the same reasons.

Response to Arguments

14. Applicant's arguments, see p.12-15, filed 2/3/03, with respect to the rejection(s)of claim(s) 1 and 2 under 35 USC 112, first paragraph (Written Description) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of 35 USC 101 (Utility) and 35 USC 112, first paragraph (Enablement). See above.

15. Applicant's arguments, see p.15-17, filed 2/3/03, with respect to the rejection(s)of claim(s) 1 and 2 under 35 USC 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of 35 USC 101 (Utility) and 35 USC 112, first paragraph (Enablement). See above.

16. The amendment to claim 6 has obviated the previous rejection under 35 112, second paragraph. However, the amended claim is now rejected under 35 USC 112, second paragraph for the reasons set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
April 21, 2003